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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 7/06	A1	(11) International Publication Number: WO 96/26705 (43) International Publication Date: 6 September 1996 (06.09.96)
(21) International Application Number: PCT/US96/02791 (22) International Filing Date: 27 February 1996 (27.02.96) (30) Priority Data: 08/396,426 28 February 1995 (28.02.95) US (60) Parent Application or Grant (63) Related by Continuation US 08/396,426 (CON) Filed on 28 February 1995 (28.02.95) (71) Applicant (for all designated States except US): HANDELMAN, Joseph, H. [US/US]; 26 West 61st Street, New York, NY 10023 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): AHLUWALIA, Gurpreet, S. [US/US]; 8632 Stable View Court, Gaithersburg, MD 20879 (US). (74) Agents: GALLOWAY, Peter, D.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: REDUCTION OF HAIR GROWTH		
(57) Abstract Mammalian hair growth is reduced by applying to the skin a dermatologically acceptable composition including a catechin compound.		

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- 1 -

REDUCTION OF HAIR GROWTH

The invention relates to a method of reducing unwanted hair growth in mammals.

5 A main function of mammalian hair is to provide environmental protection. However, that function has largely been lost in humans, in whom hair is kept or removed from various parts of the body essentially for cosmetic reasons. For example, it is generally preferred to have hair on the scalp but not
10 on the face.

Various procedures have been employed to remove unwanted hair, including shaving, electrolysis, depilatory creams or lotions, waxing, plucking, and therapeutic antiandrogens. These conventional
15 procedures generally have drawbacks associated with them. Shaving, for instance, can cause nicks and cuts and can also promote the perception of an increase in the rate of hair regrowth. Shaving also can leave stubble. Electrolysis, on the other hand, can keep a
20 treated area free of hair for prolonged periods of time, but can be expensive, painful, and sometimes leaves scarring. Depilatory creams, though very effective, typically are not recommended for frequent use due to their high irritancy potential. Waxing and
25 plucking can cause pain, discomfort, and poor removal of short hair. Finally, antiandrogens -- which have been used to treat female hirsutism -- can have unwanted side effects.

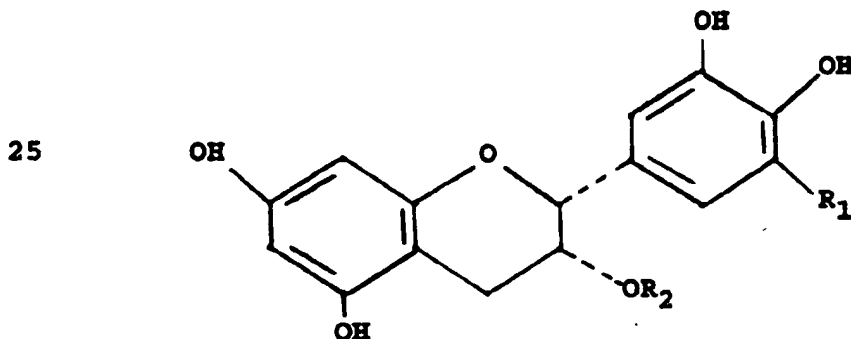
Green tea is a common beverage consumed

- 2 -

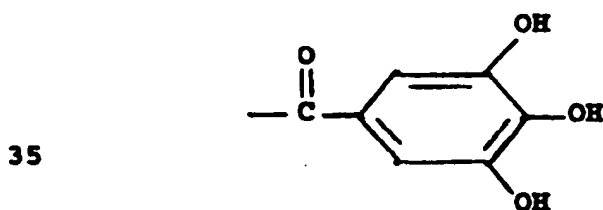
throughout the world, particularly in Asian countries. The tea leaves contain such chemically active components as flavanols, flavonoids, and phenolic acids. These components may represent as much as 1/3 the dry weight of green tea leaves. The catechins present in the leaves are from the chemical class polyphenols. Four major catechins have been isolated from the leaves: epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate.

It has now been found that unwanted mammalian (including human) hair growth -- particularly androgen-stimulated hair growth -- can be reduced by applying to the skin a dermatologically acceptable composition including a catechin compound in an amount effective to reduce hair growth. The unwanted hair growth which is reduced may be normal hair growth, or hair growth that results from an abnormal or diseased condition. The preferred catechin compounds are the four major catechin compounds present in green tea leaves.

A "catechin compound", as used herein, is a compound that includes the following ring structure



30 For (-)-epicatechin (EC), R_1 and R_2 are H. For (-)-epicatechin gallate (ECG), R_1 is H and R_2 is



- 3 -

For (-)-epigallocatechin (EGC), R_1 is OH and R_2 is H. And for (-)-epigallocatechin gallate (EGCG), R_1 is OH and R_2 is the same as in (-)-epicatechin gallate (ECG). Other catechin compounds include afzelchin, gallocatechin, catechin oligomers (procyanidins), and oxidative dimers of catechin (theaflavin, theaflavin monogallate, theaflavin digallate). In addition, "catechin compound", as used herein, encompasses compounds in which one or more of the hydroxy groups in the above ring structure are replaced by ester groups (e.g., alkyl esters such as methyl and ethyl esteric).

Epicatechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate were isolated from green tea leaves according to the procedure described by R. Agarwal et al., Cancer Research 52:3582-3588 (1992), with some modification. Dried green tea leaves were extracted with hot water at 80°C. under nitrogen. The hot water extraction was repeated twice. The residual leaves were further extracted with 80% ethanol by gently agitating at 25-30°C. on a horizontal shaker at 125 rpm for 1 hr. The water and the ethanol extracts were combined. The hydro-alcoholic (water-ethanol) extract was treated with chloroform to remove caffeine and pigments. The chloroform layer was separated from the hydro-alcoholic layer using a separatory funnel. The latter fraction was extracted three times under nitrogen with ethyl acetate. The ethyl acetate layer was separated and subjected to rotary evaporation to remove the organic solvent. The residue was dissolved in water and freeze-dried. This resulted in an off-white to slightly yellow dried residue of green tea polyphenols (GTP). The total yield of the polyphenolic fraction was 10.3%. The percent composition of individual polyphenol component in the mixture was determined on a reverse-phase HPLC system. The HPLC analysis revealed four major catechin components in the mixture: epigal-

- 4 -

locatchin (4.6%), epigallocatechin gallate (69.6%),
epicatechin (6.7%) and epicatechin gallate (19.1%).

The individual catechin components were
further purified on a preparative reverse phase HPLC
5 system. The freeze-dried GTP's fraction was dissolved
in water, and loaded on to a 40 x 300mm C-18 reverse
phase column. The catechin compounds were eluted from
the column using a gradient elution with water
(adjusted to pH 4.4 with formic acid) and ethanol. The
10 column eluent was collected at 1 min intervals HPLC
fractions containing purified epigallocatechin,
epigallocatechin gallate, epicatechin, and epicatechin
gallate (as verified using analytical reverse phase
system) were pooled and freeze-dried.

15 The catechin compound preferably is
incorporated in a topical composition which includes a
non-toxic dermatologically acceptable vehicle or
carrier which is adapted to be spread upon the skin.
Examples of suitable vehicles are acetone, alcohols, or
20 a cream, lotion, or gel which can effectively deliver
the active compound. One such vehicle is disclosed in
co-pending application PCT/US93/0506A. In addition, a
penetration enhancer may be added to the vehicle to
further enhance the effectiveness of the formulation.

25 The concentration of the catechin compound in
the composition may be varied over a wide range up to a
saturated solution, preferably from 0.1% to 40% by
weight or even more; the reduction of hair growth
increases as the amount of the catechin compound
30 applied increases per unit area of skin. A catechin
compound can be used in purified form or as a mixture;
for example the mixture of catechin compounds isolated
from green tea leaves as previously described can be
used with or without further purification. The maximum amount
35 effectively applied is limited only by the rate at
which the catechin compound penetrates the skin.
Generally, the effective amounts range from 100 to 3000

- 5 -

micrograms or more per square centimeter of skin.

The composition should be topically applied to a selected area of the body from which it is desired to reduce hair growth. For example, the composition can be applied to the face, particularly to the beard area of the face, i.e., the cheek, neck, upper lip, and chin. The composition can also be applied to the legs, arms, torso or armpits. The composition is particularly suitable for reducing the growth of unwanted hair in women suffering from hirsutism or other conditions. In humans, the composition should be applied once or twice a day, or even more frequently, for at least three months to achieve a perceived reduction in hair growth. Reduction in hair growth is demonstrated when the frequency of hair removal (shaving, tweezing, depilatory use, waxing) is reduced, or the subject perceives less hair on the treated site, or quantitatively, when the weight of hair removed by shaving (i.e., hair mass) is reduced. Benefits of reduced hair removal frequency include convenience and less skin irritation.

Male intact Golden Syrian hamsters are considered acceptable models for human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8 mm. in major diameter, which grow thick black and coarse hair similar to human beard hair. These organs produce hair in response to androgens in the hamster. To evaluate the effectiveness of a particular catechin compound, or mixture of catechin compound, the flank organs of each of a group of hamsters are depilated by applying a thioglycolate based chemical depilatory (Surgex). To one organ of each animal 10-25 μ l. of vehicle alone once a day is applied, while to the other organ of each animal an equal amount of vehicle containing a catechin compound is applied.

After thirteen applications (one application

- 6 -

p r day for fiv days a week), the flank organs are shaved and the amount of recovered hair (hair mass) from each is weighed. Percent-reduction of hair growth is calculated by subtracting the hair mass (mg) value of the test compound treated side from the hair mass value of the vehicle treated side; the delta value obtained is then divided by the hair mass value of the vehicle treated side, and the resultant number is multiplied by 100.

10 The above-described assay will be referred to herein as the "Golden Syrian hamster" assay. Preferred compositions provide a reduction in hair growth of at least about 35%, more preferably at least about 50%, and most preferably at least about 70% when tested in
15 the Golden Syrian hamster assay.

The mixture of catechins isolated from green tea leaves as described previously were tested in the Golden Syrian hamster assay. The mixture caused a dose dependent reduction of hair growth in the range of 46-
20 91%. The mixture was tested at a 5, 10, 20 and 30% dose. The results are presented in Table 1.

TABLE 1

Reduction of Hair Growth Using Mixture of Catechin Compounds

Treatment	Vehicle	Dose	pH	<u>Hair Mass(mg) + SEM</u>		<u>%Inhibition</u>
				<u>Untreated</u>	<u>Treated</u>	
Mixture	A ¹	5%	5.0	2.29±.21	1.25±.17	46±7
Mixture	A	10%	4.5	2.21±.17	0.58±.11	73±5
Mixture	A	20%	5.0	2.84±.21	0.42±.10	85±4
Mixture	A	30%	5.0	2.34±.21	0.25±.13	91±5
Control	A	NA ²	4.6	2.20±.18	2.35±.20	NI ³

¹ Vehicle A: Pure water (68%), ethanol (16%), propylene glycol (5%), dipropylene glycol (5%), benzyl alcohol (4%) and propylene carbonate (2%)

² NA: Not applicable

³ NI: No inhibition

- 8 -

Epigallocatechin (EGC), epigallocatechin gallate (EGCG), epicatechin (EC), and epicatechin gallate (ECG), purified as described previously, also were tested in a Golden Syrian hamster assay. The results are presented in Table 2. Among the four catechins, epigallocatechin gallate was found to be the most potent. The hair growth reductions ranged from 58 to 81%. In a dose response study, this compound was found to be quite effective even at a 1% concentration, which produced a 53% hair growth reduction.

TABLE 2
Reduction of Hair Growth by Purified Catechin Compounds

Tr atment	Vehicle	Dose	pH	<u>Hair Mass(mg) + SEM</u>		<u>%Inhibition</u>
				<u>Untreated</u>	<u>Treated</u>	
EGCG	A ¹	1%	3.5	2.74±.30	1.26±.12	53±47
EGCG	A	2.5%	3.5	2.32±.09	0.98±.14	58±6
EGCG	A	5%	3.5	2.16±.30	0.45±.11	67±15
EGCG	A	10%	3.5	2.62±.24	0.45±.25	81±11
ECG	A	10%	4.5	2.94±.50	0.64±.14	73±7
EGC	A	10%	3.5	2.15±.33	0.57±.17	65±12
EC	A	10%	3.5	1.94±.25	0.74±.17	58±9
Control	A	NA ²	4.0	2.39±.21	2.44±.38	NI ³

¹ Vehicle A: Pure water (68%), ethanol (16%), propylene glycol (5%), dipropylene glycol (5%), benzyl alcohol (4%) and propylene carbonate (2%)

² NA: Not applicable

³ NI: No inhibition

- 10 -

It will be appreciated by those skilled in the art that the invention can be performed within a wide range of equivalent parameters of composition and conditions without departing from the spirit or scope
5 of the invention or of any embodiment thereof.

- 11 -

C L A I M S

1. A method of reducing mammalian hair growth, comprising
selecting an area of skin from which reduced
5 hair growth is desired; and
applying to said area of skin a
dermatologically acceptable composition including a
catechin compound in an amount effective to reduce hair
growth.
- 10 2. The method of claim 1, wherein said catechin
compound is epigallocatechin gallate.
3. The method of claim 1, wherein said catechin
compound is epicatechin gallate.
4. The method of claim 1, wherein said catechin
15 compound is epigallocatechin.
5. The method of claim 1, wherein said catechin
compound is epicatechin.
6. The method of claim 1, wherein said
composition includes a mixture of catechin compounds.
- 20 7. The method of claim 6, said method further
comprising isolating said mixture of catechin compounds
from green tea leaves.
8. The method of claim 1, wherein the
concentration of said catechin compound in said
25 composition is between 1% and 40%.
9. The method of claim 1, wherein the
composition is applied to the skin in an amount of from
100 to 4000 micrograms of said catechin compound per
square centimeter of skin.
- 30 10. The method of claim 1, wherein the
composition is applied to the skin on the face of said
mammal.
11. The method of claim 1, wherein the
composition provides a reduction in hair growth of at
35 least 30% when tested in the Golden Syrian hamster
assay.
12. The method of claim 1, wherein the

- 12 -

composition provides a reduction in hair growth of at least 50% when tested in the Golden Syrian hamster assay.

13. The method of claim 1, wherein the
5 composition provides a reduction in hair growth of at least 70% when tested in the Golden Syrian hamster assay.

14. The method of claim 1, wherein said mammal is a human.

10 15. The method of claim 1, wherein said area of skin comprises an area suffering from hirsutism.

16. The method of claim 1, wherein said composition further comprises a non-toxic, dermatologically acceptable carrier or vehicle.

15 17. The method of claim 1, wherein said catechin compound is selected from the group consisting of afzelchin, gallocatechin, catechin oligomers, and oxidative dimers of catechin.

18. A method of reducing mammalian hair growth,
20 comprising
selecting an area of skin from which reduced hair growth is desired; and

applying to said area of skin a dermatologically acceptable composition comprising
25 green tea leaves or a component extracted from green tea leaves in an amount effective to reduce hair growth.

19. The use of a catechin compound for the manufacture of a medicament for reducing mammalian hair
30 growth.

20. The use according to claim 19, wherein said compound is as defined in any one of claims 2 to 18.

21. A method of producing a composition for reducing mammalian hair growth, which comprises
35 selecting a catechin compound, and combining said compound, in an amount effective to reduce hair growth, with a non-toxic, dermatologically acceptable vehicle

- 13 -

or carrier.

22. A method according to claim 21, wherein said vehicle or carrier is adapted to be spread upon the skin of a mammal.

5 23. A method according to claim 21, wherein said compound is as defined in any one of claims 2 to 18.

24. The new use of a catechin compound for reducing hair growth.

25. A composition when used for inhibiting
10 mammalian hair growth, which includes a catechin compound in an amount effective to reduce hair growth and a non-toxic, dermatologically acceptable vehicle or carrier.

26. A composition according to claim 25, wherein
15 said compound is as defined in any one of claims 2 to 18.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 96/02791A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR,A,2 527 927 (KAO CORPORATION) 9 December 1983 see page 1 - page 4, line 30; claims 1-3,6,7	1-24
X	---	25,26
A	FR,A,2 708 851 (L'OREAL) 17 February 1995 see the whole document	1-24
X	---	25,26
A	WO,A,93 24106 (J. COTTERET) 9 December 1993 see claims 1,2,16	1-24
X	---	25,26

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

1 August 1996

Date of mailing of the international search report

09.08.96

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INTERNATIONAL SEARCH REPORT

Internat. Application No.
PCT/US 96/02791

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 107, no. 16, 19 October 1987 Columbus, Ohio, US; abstract no. 140869, T. SAKAMOTO: "Hair preparation containing tannins and bactericides" XP002009948 see abstract	1-24
X	& JP,A,62 053 917 (SHISEIDO CO., LTD.) 9387	25,26
A	--- CHEMICAL ABSTRACTS, vol. 114, no. 16, 22 April 1991 Columbus, Ohio, US; abstract no. 149913, T. IKEDA: "Catechins for preventing deterioration of cosmetics, food and pharmaceuticals due to the sunlight." XP002009949 see abstract	24,25
X	& JP,A,02 202 581 (SHISEIDO CO., LTD.) 10 August 1990 -----	25,26

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/US 96/02791

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A-2527927	09-12-83	JP-A- 59051209 CA-A- 1201978 DE-A- 3320539 GB-A,B 2121281 US-A- 4517175	24-03-84 18-03-86 08-12-83 21-12-83 14-05-85
FR-A-2708851	17-02-95	NONE	
WO-A-9324106	09-12-93	NONE	